Determination of antimicrobial susceptibility test breakpoints

European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

INTRODUCTION

This document is the first full description of the method of determining clinical breakpoints for antibiotics (for definitions of terminology, see *Clinical Microbiology and Infection*, 1998; 4: 291–6) that has been used for the past 10 years by the European Study Group on Breakpoints (ESGAB) and now to be used by EUCAST, its successor. Because of the diversity of methodology of susceptibility testing in Europe, particularly in disk methods, we have determined breakpoints only in relation to MICs. Informal assessment has shown that MICs for common non-fastidious bacteria, competently determined by the methods described by a number of national societies, are very close and often identical. We are in the process of formal study of this comparability.

In order to determine breakpoints, the EUCAST Breakpoints Subcommittee requires information from those promoting the antimicrobial agent. In the pursuit of international collaboration, we have, whenever possible, used the wording of a version of the NCCLS document M23 which was the subject of discussion at the time the EUCAST document was produced. The wording of this EUCAST document differs from that of the published versions of M23 and cannot be used as a substitute when it is intended to follow NCCLS guidelines. Rather, its purpose is to facilitate the provision of documentation required of those seeking a breakpoint determination in Europe.

Information required for the determination of antimicrobial susceptibility test breakpoints

In vitro drug characteristics

Information is required on the use of diluents and solvents; preparation of stock solutions; stability of the drug in appropriate concentrations at storage and incubation temperature; and the relationship or comparability of MIC endpoints defined by different methods, for broth and agar methods and media, for relevant representative organisms.

Distribution of susceptibility of organisms

MICs must be determined on at least 500 isolates (and at least 300 anaerobes in addition if relevant, each species in sufficient numbers to establish norms, with a note on relative prevalence among clinical isolates), which must include examples of clinically relevant species appropriate to the class of compound and its proposed clinical use. They must include isolates showing important resistance mechanisms. For example, methicillin-resistant *Stapylococcus aureus* (MRSA) and coagulase-negative staphylococci should be included for the evaluation of antistaphylococcal agents.

The MIC distributions must be shown (not MIC_{50}, MIC_{90}, etc.), and compared with those obtained for recent clinical isolates obtained from large geographically diverse surveys.

Pharmacokinetics and pharmacodynamics

Methods for measurement of drug concentrations in serum and body fluids must be provided. If bioassay and other methods are available, their relative performance must be shown.

Actual plots must be provided of serum or plasma levels in humans over time following expected dosages and methods of administration. Concentrations in cerebrospinal fluid must be presented if the drug is to be used for the treatment of meningitis. If available, data from target patient populations should be presented. The number of subjects or patients, characteristics, and intra-and inter-individual variability of measurments must be included.

Pharmacokinetic parameters that are also useful for simulation, calculation of pharmacokinetic/pharmacodynamic relationships, and comparisons with other drugs of the same class must be provided. These parameters must include bioavailability, C_{max}, AUC, volume of distribution, protein binding (and its effect on MIC and pharmacokinetic and pharmacodynamic parameters), metabolism (including data on microbiological activity of metabolites), excretion (with kinetics and effects of pH and cations in urine, if relevant), clearance, and elimination half-life. The number of subjects should be governed by good statistical assessments.

Data on differences in AUC, expected peak and trough serum concentrations, and pharmacokinetic/pharmacodynamic parameters (e.g. AUC: proposed MIC breakpoint ratio) with anticipated dosage regimens are helpful, if available. As well as data on normal human subjects, data on target populations which might include children, the elderly and populations with special dosage requirements (e.g. in renal or hepatic failure) are desirable.

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An analysis of the relationship between pharmacokinetic and pharmacodynamic parameters and efficacy must be included. Serum concentrations resulting from proposed dosage regimens in humans should be used. The analysis might include (but not be limited to): the time for which serum or plasma levels exceed the MIC of relevant (including anaerobic and fastidious) organisms; peak serum or plasma level/MIC ratio; and area under the drug serum concentration (AUC)/MIC ratio. Similar calculations for related drugs of the same class should be provided. Data for this analysis might be derived from experimental models of infection, from humans given proposed dosage schedules, or from clinical studies. Data on the postantibiotic effect and on the impact of increasing drug concentrations on bacterial killing may be helpful.

When basic information has been collected on the *in vitro* activity of the drug, distribution of MICs and pharmacokinetics/pharmacodynamics, it will be desirable to establish tentative breakpoints.

Correlation of test results with clinical outcome

During the clinical evaluation of antimicrobial agents, clinical cure and bacterial eradication rates must be correlated with appropriate *in vitro* tests results to confirm the validity of the proposed interpretive criteria. There may be occasions when a clear breakpoint can be determined from the clinical data. In other situations, the clinical data will serve more to support other types of data (microbiological and pharmacokinetic/pharmacodynamic) in determining interpretive criteria.

In the course of development of an antimicrobial agent, the manufacturer will conduct clinical studies that will yield a large volume of data. Optimally, the design and evaluation of studies should conform to the most recent guidelines of ESCMID and IDSA. The manufacturer must provide, in a summarized fashion, all relevant data needed to make breakpoint determinations. The manufacturer should note if the data are different from those submitted to regulatory authorities, and give reasons for the differences.

The following points should be considered:

A clear description of the clinical protocols must be given, including:

- description of the population studied;
- specific inclusion/exclusion criteria;
- dosage and duration of study and comparative drug therapy;
- times of initial, on-therapy and follow-up microbiological and clinical assessments, visits and test of cure evaluability criteria;
- definitions of 'clinical' and 'bacteriological' response.

When the category 'improved' is used as a clinical outcome, this must be clearly defined:

If adjunctive therapy is permitted, this must be so stated.

If patients are permitted to switch from the study antimicrobial regimen to another (e.g. parenteral to oral switch), this must be so stated, and criteria for such a change clearly defined.

If surgical procedures are part of the routine care of an infection type, details of such procedures within the study must be discussed.

All clinical data relevant to breakpoint analysis, including an analysis of evaluable cases and an intent-to-treat analysis of microbiologically documented cases, must be presented. In addition, summary results for the comparative arms must be presented by individual study. To allow optimal evaluation, clinical data must be presented separately for sites and types of infection (e.g. urinary tract infection, complicated or uncomplicated; pneumonia, community acquired or nosocomial). In addition, subsets of patients with bacteremia must be presented. The data analysis must be based on responses at the 'test of cure' and at the subsequent long-term follow-up visits. All failures must be carried forward to subsequent evaluations.

The data presented must be relevant to the anticipated use of the agent in clinical practice, and the organisms must be relevant to the clinical site of infection studied.

All clinical and/or microbiological failures must be presented separately according to the infecting bacterium, MIC and site of infection.

In vitro data must be presented as MICs, not simply as 'susceptible' or 'resistant', for individual bacterial species relevant to the anticipated use of the drug. Quality control data must be generated and recorded for all clinical isolate susceptibility determinations.

Infections due to single or predominant pathogens must be presented separately from true polymicrobial infections.

Data must be presented for both clinical (cure, improved, failure) and bacterial responses. When the category 'improved' is used, clinical response data must be broken down into separate 'cure', "improved" and 'failure' categories. Bacteriologic response data must be presented with and without 'presumed' outcomes included. In addition, data must be presented for each MIC.

Information about species or isolates that are resistant or have MICs near the proposed breakpoint is of particular interest and should be presented, for both evaluable and intent-to-treat populations.

When an antimicrobial is developed that is a combination product, then a justification for the selected ratios or concentrations must be presented.

Quality control

During the drug development process, testing of recognized quality control strains must be performed to establish preliminary and subsequently definitive quality control limits and

to determine the impact of procedural variations on test performance. Testing must be performed with all appropriate methods to establish equivalency of methods (e.g. agar, dilution and broth microdilution). Such testing may be carried out in one laboratory.

Resolving differences

Numerous bodies independently establish interpretive criteria and quality control limits based on evaluation of extensive data. These independent processes can produce interpretations that are discrepant. Every effort must be made to resolve such discrepancies.

REVISIONS

This document was approved by EUCAST in August 2000. Revisions will be considered by the Breakpoints Sub-committee of EUCAST during 2001. Proposals for changes should be sent to EUCAST via EUCAST Secretariat, Cornelia Hasselman, Martin-Buber-Weg 17, D-81245 Munich, Germany (Tel: + 49 89 8971 2003, Fax: + 49 89 8971 2004; E-mail: Cornelia.Hasselman@t-online.de).

Since parts of this document are similar to selected sections of NCCLS document M23, and in recognition of the years of effort on the part of NCCLS and its Subcommittee on Antimicrobial Susceptibility Testing, we sought the agreement of NCCLS on utilization of this text. NCCLS has granted permission for such adaptation of its M23 (Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters) guideline. Copies of the current M23 edition may be obtained from NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

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